View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

Structure, Vol. 9, R73–R77, July, 2001, ©2001 Elsevier Science Ltd. All rights reserved. PII S0969-2126(01)00625-6

# Paper Alert

Chosen by **Robert Liddington,* Christin Frederick,† Stephen D. Fuller,‡ and Sophie Jackson§**
*Program on Cell Adhesion
The Burnham Institute
10901 North Torrey Pines Road
La Jolla, California 92037
†Laboratory of X-ray Crystallography
Dana-Farber Cancer Institute
44 Binney Street
Boston, Massachusetts 02115
‡Division of Structural Biology
Wellcome Trust Centre for Human Genetics
Henry Wellcome Building for Genomic Medicine
Roosevelt Drive
Headington, Oxford
OX3 7BN
United Kingdom
§Department of Chemistry
University of Cambridge
Lensfield Road
Cambridge CB2 1EW
United Kingdom

A selection of interesting papers that were published in the month before our press date in major journals most likely to report significant results in structural biology, protein and RNA folding.

☐ **Structural basis of the redox switch in the OxyR transcription factor.** Hee-Jung Choi, Seung-Jun Kim, Partha Mukhopadhyay, Sayeon Cho, Joo-Rang Woo, Gisela Storz, and Seong-Eon Ryu (2001). Cell *105*, 103–113.

The *Escherichia coli* OxyR transcription factor senses $H_2O_2$ and is activated through the formation of an intramolecular disulfide bond. The authors present the crystal structures of the regulatory domain of OxyR in its reduced and oxidized forms, determined at 2.7 Å and 2.3 Å resolutions, respectively. In the reduced form, the two redox-active cysteines are separated by approximately 17 Å. Disulfide bond formation in the oxidized form results in a significant structural change in the regulatory domain. The structural remodeling, which leads to different oligomeric associations, accounts for the redox-dependent switch in OxyR and provides a novel example of protein regulation by "fold editing" through a reversible disulfide bond formation within a folded domain.

☐ **Structure of Pumilio reveals similarity between RNA and peptide binding motifs.** Thomas A. Edwards, Scott E. Pyle, Robin P. Wharton, and Aneel K. Aggarwal (2001). Cell *105*, 281–289.

Translation regulation plays an essential role in the differentiation and development of animal cells. One well-studied case is the control of hunchback mRNA during early *Drosophila* embryogenesis by the trans-acting factors Pumilio, Nanos, and Brain Tumor. The authors report here a crystal structure of the critical region of Pumilio, the Puf domain, that organizes a multivalent repression complex on the 3′ untranslated region of hunchback mRNA. The structure reveals an extended, rainbow-shaped molecule, with tandem helical repeats that bear unexpected resemblance to the armadillo repeats in β-catenin and the HEAT repeats in protein phosphatase 2A. The authors identify putative interaction surfaces for hunchback mRNA and the cofactors Nanos and Brain Tumor.

☐ **Specificity determinants in phosphoinositide dephosphorylation: crystal structure of an archetypal inositol polyphosphate 5-phosphatase.** Yosuke Tsujishita, Shuling Guo, Leslie E. Stolz, John D. York, and James H. Hurley (2001). Cell *105*, 379–389.

Inositol polyphosphate 5-phosphatases are central to intracellular processes ranging from membrane trafficking to $Ca^{2+}$ signaling, and defects in this activity result in the human disease Lowe syndrome. The 1.8 Å resolution structure of the inositol polyphosphate 5-phosphatase domain of SPsynaptojanin bound to $Ca^{2+}$ and inositol (1,4)-bisphosphate reveals a fold and an active site His and Asp pair resembling those of several $Mg^{2+}$-dependent nucleases. Additional loops mediate specific inositol polyphosphate contacts. The 4-phosphate of inositol (1,4)-bisphosphate is misoriented by 4.6 Å compared to the reactive geometry observed in the apurinic/apyrimidinic endonuclease 1, explaining the dephosphorylation site selectivity of the 5-phosphatases.

☐ **The structure of the β-catenin/E-cadherin complex and the molecular basis of diverse ligand recognition by β-catenin.** Andrew H. Huber and William I. Weis (2001). Cell *105*, 391–402.

As a component of adherens junctions and the Wnt signaling pathway, β-catenin binds cadherins, Tcf family transcription factors, and the tumor suppressor APC. The authors have determined the crystal structures of both unphosphorylated and phosphorylated E-cadherin cytoplasmic domain complexed with the arm repeat region of β-catenin. The interaction spans all 12 arm repeats, and features quasi-independent binding regions that include helices which interact with both ends of the arm repeat domain and an extended stretch of 14 residues which closely resembles a portion of XTcf-3. Phosphorylation of E-cadherin results in interactions with a hydrophobic patch of β-catenin that mimics the binding of an amphipathic XTcf-3 helix. APC contains sequences homologous to the phosphorylated region of cadherin and is predicted to bind similarly.

□ **Structural biochemistry and interaction architecture of the DNA double-strand break repair Mre11 nuclease and Rad50-ATPase.** Karl-Peter Hopfner, Annette Karcher, Lisa Craig, Tammy T. Woo, James P. Carney, and John A. Tainer (2001). Cell *105*, 473–485.

To clarify functions of the Mre11/Rad50 (MR) complex in DNA double-strand break repair, the authors report *Pyrococcus furiosus* Mre11 crystal structures, revealing a protein phosphatase-like, dimanganese binding domain capped by a unique domain controlling active site access. These structures unify Mre11's multiple nuclease activities in a single endo/exonuclease mechanism and reveal eukaryotic macromolecular interaction sites by mapping human and yeast Mre11 mutations. Furthermore, the structure of the *P. furiosus* Rad50 ABC-ATPase with its adjacent coiled-coil defines a compact Mre11/Rad50-ATPase complex and suggests that Rad50-ATP-driven conformational switching directly controls the Mre11 exonuclease.

□ **Solution structure of the methyl-CpG binding domain of human MBD1 in complex with methylated DNA.** Izuru Ohki, Nobuya Shimotake, Naoyuki Fujita, Jun-Goo Jee, Takahisa Ikegami, Mitsuyoshi Nakao, and Masahiro Shirakawa (2001). Cell *105*, 487–497.

In vertebrates, the biological consequences of DNA methylation are often mediated by protein factors containing conserved methyl-CpG binding domains (MBDs). Mutations in the MBD protein MeCP2 cause the neurodevelopmental disease Rett syndrome. The authors report the solution structure of the MBD of the human methylation-dependent transcriptional regulator MBD1 bound to methylated DNA. DNA binding causes a loop in MBD1 to fold into a major and novel DNA binding interface. Recognition of the methyl groups and CG sequence at the methylation site is due to five highly conserved residues that form a hydrophobic patch. The structure indicates how MBD may access nucleosomal DNA without encountering steric interference from core histones, and provides a basis to interpret mutations linked to Rett syndrome in MeCP2.

□ **Crystal Structure of a Pumilio homology domain.** Xiaoqiang Wang, Phillip D. Zamore, and Traci M. Tanaka Hall (2001). Mol. Cell *7*, 855–865.

Puf proteins regulate translation and mRNA stability by binding sequences in their target RNAs through the Pumilio homology domain (PUM-HD), which is characterized by eight tandem copies of a 36 amino acid motif, the PUM repeat. The authors have solved the structure of the PUM-HD from human Pumilio1 at 1.9 Å resolution. The structure reveals that the eight PUM repeats correspond to eight copies of a single repeated structural motif. The PUM repeats pack together to form a right-handed superhelix that approximates a half doughnut. The distribution of side chains on the inner and outer faces of this half doughnut suggests that the inner face of the PUM-HD binds RNA while the outer face interacts with proteins such as Nanos, Brain Tumor, and cytoplasmic polyadenylation element binding protein.

□ **Crystal structure of the atypical protein kinase domain of a TRP channel with phosphotransferase activity.** Hiroto Yamaguchi, Masayuki Matsushita, Angus C. Nairn, and John Kuriyan (2001). Mol. Cell *7*, 1047–1057.

Transient receptor potential (TRP) channels modulate calcium levels in eukaryotic cells in response to external signals. A novel transient receptor potential channel has the ability to phosphorylate itself and other proteins on serine and threonine residues. The catalytic domain of this channel kinase has no detectable sequence similarity to classical eukaryotic protein kinases and is essential for channel function. The structure of the kinase domain, reported here, reveals unexpected similarity to eukaryotic protein kinases in the catalytic core as well as to metabolic enzymes with ATP-grasp domains. The inclusion of the channel kinase catalytic domain within the eukaryotic protein kinase superfamily indicates a significantly wider distribution for this group of signaling proteins than suggested previously by sequence comparisons alone.

□ **The homing endonuclease I-CreI uses three metals, one of which is shared between the two active sites.** Brett S. Chevalier, Raymond J. Monnat, Jr., and Barry L. Stoddard (2001). Nat. Struct. Biol. *8*, 312–316.

Homing endonucleases, like restriction enzymes, cleave double-stranded DNA at specific target sites. The cleavage mechanism(s) utilized by LAGLIDADG endonucleases have been difficult to elucidate; their active sites are divergent. The authors report two high resolution structures of the dimeric I-CreI homing endonuclease bound to DNA: a substrate complex with calcium and a product complex with magnesium. The bound metals in both complexes are verified by manganese anomalous difference maps. The active sites are positioned close together to facilitate cleavage across the DNA minor groove; each contains one metal ion bound between a conserved aspartate (Asp 20) and a single scissile phosphate. A third metal ion bridges the two active sites. These structures illustrate that a unique variant of a two-metal endonuclease mechanism is employed by the highly divergent LAGLIDADG enzyme family.

□ **The leukemia-associated AML1 (Runx1)–CBFβ complex functions as a DNA-induced molecular clamp.** Jerónimo Bravo, Zhe Li, Nancy A. Speck, and Alan J. Warren (2001). Nat. Struct. Biol. *8*, 371–378.

The authors have determined the structure, at 2.6 Å resolution, of the AML1 (Runx1) Runt domain–CBFβ–DNA ternary complex, the most common target for mutations in human leukemia. The structure reveals that the Runt domain DNA binding mechanism is unique within the p53 family of transcription factors. The extended C-terminal "tail" and "wing" elements adopt a specific DNA-bound conformation that clamps the

phosphate backbone between the major and minor grooves of the distorted B-form DNA recognition site. Furthermore, the extended "tail" mediates most of the NF-κB/Rel-like base-specific contacts in the major groove. The structure clearly explains the molecular basis for the loss of DNA binding function of the Runt domain–CBFβ complex as a consequence of the human disease-associated mutations in leukemogenesis and cleidocranial dysplasia.

☐ **Crystal structure of a bifunctional transformylase and cyclohydrolase enzyme in purine biosynthesis.** Samantha E. Greasley, Patricia Horton, Joseph Ramcharan, G. Peter Beardsley, Stephen J. Benkovic, and Ian A. Wilson (2001). Nat. Struct. Biol. *8*, 402–406.

ATIC, the product of the *purH* gene, is a 64 kDa bifunctional enzyme that possesses the final two activities in de novo purine biosynthesis, AICAR transformylase and IMP cyclohydrolase. The crystal structure of avian ATIC has been determined to 1.75 Å resolution by the MAD method using a Se-methionine modified enzyme. ATIC forms an intertwined dimer with an extensive interface of ~5,000 Å$^2$ per monomer. Each monomer is composed of two novel, separate functional domains. The N-terminal domain (up to residue 199) is responsible for the IMPCH activity, whereas the AICAR Tfase activity resides in the C-terminal domain (200–593). The active sites of the IMPCH and AICAR Tfase domains are ~50 Å apart, with no structural evidence of a tunnel connecting the two active sites.

☐ **Solution structure of a Nedd4 WW domain–ENaC peptide complex.** Voula Kanelis, Daniela Rotin, and Julie D. Forman-Kay (2001). Nat. Struct. Biol. *8*, 407–412.

Nedd4 is a ubiquitin protein ligase composed of a C2 domain, three (or four) WW domains, and a ubiquitin ligase Hect domain. Nedd4 was demonstrated to bind the epithelial sodium channel (αβγENaC), by association of its WW domains with PY motifs (XPPXY) present in each ENaC subunit, and to regulate the cell surface stability of the channel. The PY motif of βENaC is deleted or mutated in Liddle syndrome, a hereditary form of hypertension caused by elevated ENaC activity. The authors report the solution structure of the third WW domain of Nedd4 complexed to the PY motif-containing region of βENaC (TLPIPGTPPPNYDSL, referred to as βP2). A polyproline type II helical conformation is adopted by the PPPN sequence. Unexpectedly, the C-terminal sequence YDSL forms a helical turn and both the tyrosine and the C-terminal leucine contact the WW domain. This is unlike other proline-rich peptides complexed to WW domains, which bind in an extended conformation and lack molecular interactions with residues C-terminal to the tyrosine or the structurally equivalent residue in non-PY motif WW domain targets.

☐ **The structure of the IgE Cε2 domain and its role in stabilizing the complex with its high-affinity receptor FcεRIα.** James M. McDonnell, Rosaleen Calvert, Rebecca L. Beavil, Andrew J. Beavil, Alistair J. Henry, Brian J. Sutton, Hannah J. Gould, and David Cowburn (2001). Nat. Struct. Biol. *8*, 437–441.

The stability of the complex between IgE and its high-affinity receptor, FcεRI, on mast cells is a critical factor in the allergic response. The long half-life of the complex of IgE bound to this receptor in situ (~2 weeks, compared with only hours for the comparable IgG complex) contributes to the permanent sensitization of these cells and, hence, to the immediate response to allergens. Here we show that the second constant domain of IgE, Cε2, which takes the place of the flexible hinge in IgG, contributes to this long half-life. When the Cε2 domain is deleted from the IgE Fc fragment, leaving only the Cε3 and Cε4 domains (Cε3–4 fragment), the rate of dissociation from the receptor is increased by greater than one order of magnitude. The authors report the structure of the Cε2 domain by heteronuclear NMR spectroscopy and show by chemical shift perturbation that it interacts with FcεRIα. Interactions of Cε2 with both FcεRIα and Cε3–4 provide a structural explanation for the exceptionally slow dissociation of the IgE–FcεRIα complex.

☐ **The structure of ADP-ribose pyrophosphatase reveals the structural basis for the versatility of the Nudix family.** Sandra B. Gabelli, Mario A. Bianchet, Maurice J. Bessman, and L. Mario Amzel (2001). Nat. Struct. Biol. *8*, 467–472.

Regulation of cellular levels of ADP-ribose is important in preventing nonenzymatic ADP-ribosylation of proteins. The *Escherichia coli* ADP-ribose pyrophosphatase, a Nudix enzyme, catalyzes the hydrolysis of ADP-ribose to ribose-5-P and AMP, compounds that can be recycled as part of nucleotide metabolism. The structures of the apo enzyme, the active enzyme and the complex with ADP-ribose were determined to 1.9 Å, 2.7 Å, and 2.3 Å, respectively. The structures reveal a symmetric homodimer with two equivalent catalytic sites, each formed by residues of both monomers, requiring dimerization through domain swapping for substrate recognition and catalytic activity. The structures also suggest a role for the residues conserved in each Nudix subfamily. The Nudix motif residues, folded as a loop-helix-loop tailored for pyrophosphate hydrolysis, compose the catalytic center; residues conferring substrate specificity occur in regions of the sequence removed from the Nudix motif.

☐ **Crystal structure of *cis*-prenyl chain elongating enzyme, undecaprenyl diphosphate synthase.** Masahiro Fujihashi, Yuan-Wei Zhang, Yoshiki Higuchi, Xiao-Yuan Li, Tanetoshi Koyama, and Kunio Miki (2001). Proc. Natl. Acad. Sci. USA *98*, 4337–4342. Published online before print as 10.1073/pnas.071514398.

Undecaprenyl diphosphate synthase (UPS) catalyzes the *cis*-prenyl chain elongation onto trans, *trans*-farne-

syl diphosphate (FPP) to produce undecaprenyl diphosphate (UPP), which is indispensable for the biosynthesis of bacterial cell walls. The authors report the crystal structure of UPS as the only three-dimensional structure among *cis*-prenyl chain elongating enzymes. The structure is completely different from the so-called "isoprenoid synthase fold" that is believed to be a common structure for the enzymes relating to isoprenoid biosynthesis. The catalytic site comprises conserved amino acid residues located around a large hydrophobic cleft in the UPS structure and a P-loop motif, which frequently appears in the various kinds of phosphate binding sites, at the entrance of this cleft.

□ **Structure and function of the C-terminal PABC domain of human poly(A)-binding protein.** Guennadi Kozlov, Jean-François Trempe, Kianoush Khaleghpour, Avak Kahvejian, Irena Ekiel, and Kalle Gehring (2001). Proc. Natl. Acad. Sci. USA *98*, 4409–4413. Published online before print as 10.1073/pnas.071024998.

The poly(A)-binding protein (PABP) recognizes the 3′ mRNA poly(A) tail and plays an essential role in eukaryotic translation initiation and mRNA stabilization/degradation The authors have determined the solution structure of the C-terminal quarter of human poly(A)-binding protein (hPABP). The protein fragment contains a protein domain, PABC [poly(A)-binding protein C-terminal domain], which is also found associated with the HECT family of ubiquitin ligases. Chemical shift perturbation analysis was used to identify the peptide binding site in PABC and the major elements involved in peptide recognition for peptides derived from PABP interacting protein (Paip) 1, Paip2, and eRF3.

□ **X-ray structure of the human hyperplastic discs protein: An ortholog of the C-terminal domain of poly(A)-binding protein.** Rahul C. Deo, Nahum Sonenberg, and Stephen K. Burley (2001). Proc. Natl. Acad. Sci. USA *98*, 4414–4419. Published online before print as 10.1073/pnas.071552198.

PABP is a modular protein, with four N-terminal RNA-binding domains and an extensive C terminus. The C-terminal region of PABP is essential for normal growth in yeast and has been implicated in mediating PABP homo-oligomerization and protein-protein interactions. An X-ray structure of a PABP-like segment, a small, proteolytically stable, highly conserved domain within this C-terminal region, of the human HYD protein (a member of the hyperplastic discs protein family of ubiquitin ligases) has been determined at 1.04-Å resolution. The conserved domain adopts a novel fold resembling a right-handed supercoil of four $\alpha$-helices. Phylogenetic analysis of the experimentally determined (HYD) and homology modeled (PABP) protein surfaces revealed a conserved feature that may be responsible for binding to a PABP-interacting protein, Paip1, and other shared interaction partners.

□ **Crystallographic structures of the ligand-binding domains of the androgen receptor and its T877A mutant complexed with the natural agonist dihydrotestosterone.** John S. Sack, Kevin F. Kish, Chihuei Wang, Ricardo M. Attar, Susan E. Kiefer, Yongmi An, Ginger Y. Wu, Julie E. Scheffler, Mark E. Salvati, Stanley R. Krystek, Jr., Roberto Weinmann, and Howard M. Einspahr (2001). Proc. Natl. Acad. Sci. USA *98*, 4904–4909.

The structures of the ligand-binding domains (LBD) of the wild-type androgen receptor (AR) and the T877A mutant corresponding to that in LNCaP cells, both bound to dihydrotestosterone, have been refined at 2.0 Å resolution. In contrast to the homodimer seen in the retinoid-X receptor and estrogen receptor LBD structures, the AR LBD is monomeric, possibly because of the extended C terminus of AR, which lies in a groove at the dimerization interface. Binding of the natural ligand dihydrotestosterone by the mutant LBD involves interactions with the same residues as in the wild-type receptor, with the exception of residue 877, thus allowing the mutant to accommodate progesterone and other ligands that the wild-type receptor cannot.

□ **Structure of melanoma inhibitory activity protein, a member of a recently identified family of secreted proteins.** Julie C. Lougheed, James M. Holton, Tom Alber, J. Fernando Bazan, and Tracy M. Handel (2001). Proc. Natl. Acad. Sci. USA *98*, 5515–5520. Published online before print as10.1073/pnas.091601698.

Melanoma inhibitory activity (MIA) is a 12 kDa protein that is secreted from both chondrocytes and malignant melanoma cells. MIA has been reported to have effects on cell growth and adhesion, and it may play a role in melanoma metastasis and cartilage development. The authors report the 1.4 Å crystal structure of human MIA, which consists of an Src homology 3 (SH3)-like domain with N-and C-terminal extensions of about 20 aa each. The N- and C-terminal extensions add additional structural elements to the SH3 domain, forming a previously undescribed fold. MIA is a representative of a recently identified family of proteins and is the first structure of a secreted protein with an SH3 subdomain. The structure also suggests a likely protein interaction site and suggests that, unlike conventional SH3 domains, MIA does not recognize polyproline helices.

□ **The crystal structure of a heptameric archaeal Sm protein: Implications for the eukaryotic snRNP core.** Cameron Mura, Duilio Cascio, Michael R. Sawaya, and David S. Eisenberg (2001). Proc. Natl. Acad. Sci. USA *98*, 5532–5537. Published online before print as 10.1073/pnas.091102298.

Sm proteins form the core of small nuclear ribonucleoprotein particles (snRNPs), making them key components of several mRNA-processing assemblies, including the spliceosome. The authors report the 1.75-Å crystal structure of SmAP, an Sm-like archaeal protein that forms a heptameric ring perforated by a cationic

pore. In addition to providing direct evidence for such an assembly in eukaryotic snRNPs, this structure (i) shows that SmAP homodimers are structurally similar to human Sm heterodimers, (ii) supports a gene duplication model of Sm protein evolution, and (iii) offers a model of SmAP bound to single-stranded RNA (ssRNA) that explains Sm binding-site specificity. The pronounced electrostatic asymmetry of the SmAP surface imparts directionality to putative SmAP-RNA interactions.

□ **Solution structure of DFF40 and DFF45 N-terminal domain complex and mutual chaperone activity of DFF40 and DFF45.** Pei Zhou, Alexey A. Lugovskoy, John S. McCarty, Peng Li, and Gerhard Wagner (2001). Proc. Natl. Acad. Sci. USA *98*, 6051–6055.

Apoptotic DNA fragmentation is mediated by a caspase-activated DNA fragmentation factor (DFF)40. Expression and folding of DFF40 require the presence of DFF45, which also acts as a nuclease inhibitor before DFF40 activation by execution caspases. The N-terminal domains (NTDs) of both proteins are homologous, and their interaction plays a key role in the proper functioning of this two-component system. The authors report that the NTD of DFF45 alone is unstructured in solution, and its folding is induced upon binding to DFF40 NTD. Therefore, folding of both proteins regulates the formation of the DFF40/DFF45 complex. The solution structure of the heterodimeric complex between NTDs of DFF40 and DFF45 reported here shows that the mutual chaperoning includes the formation of an extensive network of intermolecular interactions that bury a hydrophobic cluster inside the interface, surrounded by intermolecular salt bridges.

□ **Structure of sortase, the transpeptidase that anchors proteins to the cell wall of *Staphylococcus aureus*.** Udayar Ilangovan, Hung Ton-That, Junji Iwahara, Olaf Schneewind, and Robert T. Clubb (2001). Proc. Natl. Acad. Sci. USA *98*, 6056–6061.

Surface proteins of Gram-positive bacteria play important roles during the pathogenesis of human infections and require sortase for anchoring to the cell-wall envelope. Sortase cleaves surface proteins at the LPXTG motif and catalyzes the formation of an amide bond between the carboxyl group of threonine (T) and the amino group of cell-wall crossbridges. The NMR structure of sortase reveals a unique β-barrel structure, in which the active-site sulfhydryl of cysteine-184 is poised for ionization by histidine-120, presumably enabling the resultant thiolate to attack the LPXTG peptide. Calcium binding near the active site stimulates catalysis, possibly by altering the conformation of a surface loop that recognizes newly translocated polypeptides.

□ **Crystal structure of the ribosome at 5.5 Å resolution.** Marat M. Yusupov, Gulnara Zh. Yusupova, Albion Baucom, Kate Lieberman, Thomas N. Earnest, J.H.D. Cate, and Harry F. Noller (2001). Science *292*, 883–896.

The authors describe the crystal structure of the complete *Thermus thermophilus* 70S ribosome containing bound messenger RNA and transfer RNAs (tRNAs) at 5.5 Å resolution. All of the 16S, 23S, and 5S ribosomal RNA (rRNA) chains, the A-, P-, and E-site tRNAs, and most of the ribosomal proteins can be fitted to the electron density map. The core of the interface between the 30S small subunit and the 50S large subunit, where the tRNA substrates are bound, is dominated by RNA, with proteins located mainly at the periphery, consistent with ribosomal function being based on rRNA. In each of the three tRNA binding sites, the ribosome contacts all of the major elements of tRNA, providing an explanation for the conservation of tRNA structure. The tRNAs are closely juxtaposed with the intersubunit bridges, in a way that suggests coupling of the 20–50 Å movements associated with tRNA translocation with intersubunit movement.

□ **Structural mechanism for statin inhibition of HMG-CoA reductase.** Eva S. Istvan and Johann Deisenhofer (2001). Science *292*, 1160–1164.

HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase (HMGR) catalyzes the committed step in cholesterol biosynthesis. Statins are HMGR inhibitors with inhibition constant values in the nanomolar range that effectively lower serum cholesterol levels and are widely prescribed in the treatment of hypercholesterolemia. The authors have determined structures of the catalytic portion of human HMGR complexed with six different statins. The statins occupy a portion of the binding site of HMG-CoA, thus blocking access of this substrate to the active site. Near the carboxyl terminus of HMGR, several catalytically relevant residues are disordered in the enzyme-statin complexes. If these residues were not flexible, they would sterically hinder statin binding.